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Disease-a-Month

Rheumatic Fever

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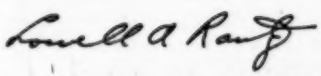
FIRST YEAR'S CONTENTS



Associate Professor of Medicine at Stanford University School of Medicine, has been affiliated with that institution since 1939. He was Field Director of the Commission on Hemolytic Streptococcal Infections of the Army Epidemiological Board, 1943-46, and conducted extensive studies of streptococcal infection and rheumatic fever in the Army during that period. Since then he has been engaged in a continuing study of streptococcal infection with special reference to the pathogenesis of rheumatic fever. His work of the last five years has been particularly devoted to the definition of the natural history of streptococcal illness in children and the immunologic responses which follow infections by streptococci. Dr. Rantz has not previously summarized his work concerning the diagnosis and treatment of rheumatic fever.

RHEUMATIC FEVER is a disease which produces disability not only because of the acute inflammatory process but also as a result of the deformities of the heart valves which so often follow. Investigation over the last 20 years has contributed much to an understanding of its etiology and pathogenesis (1).

Application of this new knowledge has led to the development of exciting new techniques that appear to be effective in the prevention of rheumatic fever. Its treatment has been modified by the introduction of adrenal steroids into therapy and by a changing point of view toward the role of salicylates and bed rest in its management. New laboratory tools have been introduced which aid in the recognition and treatment of the rheumatic state.

This monograph will summarize these important and stimulating developments, with special reference to their application at the bedside and in the clinic.

THE ETIOLOGY OF RHEUMATIC FEVER

During the past 20 years it has become apparent that infection by hemolytic streptococci is in some way related to the develop-

ment of the rheumatic state (2). The supporting evidence has been based on indirect observations and may be summarized as follows. (1) Rheumatic fever has been a sequel to known hemolytic streptococcus infections, particularly of the respiratory tract. (2) Epidemics of rheumatic fever often follow outbreaks of scarlet fever or streptococcus sore throat. (3) Recrudescences frequently appear when infection by hemolytic streptococci occurs in persons who have had previous attacks of rheumatic fever. (4) Immunologic investigations have demonstrated that high titers of various antistreptococcic antibodies are regularly demonstrable in the serum of persons with acute rheumatic fever or recurrences.

Additional information obtained during study of epidemics of hemolytic streptococcus infection in the armed forces during World War II demonstrated that rheumatic fever did indeed occur only following infection by group A hemolytic streptococci. Reports of these studies described in detail the sequence of events following infection by the hemolytic streptococcus and pointed out the great frequency and complex nature of the nonsuppurative disorders which are such common sequelae (3, 4).

The usual sequence of events begins with a hemolytic streptococcus respiratory infection which may be accompanied by sore throat, exudative tonsillitis and pharyngitis, tender anterior cervical adenitis and, occasionally, by a skin rash. Often this illness is much less typical clinically and may be exceedingly mild or even inapparent.

The acute respiratory phase of the illness subsides and is followed by a latent or quiescent period in which the patient may seem to be entirely well, although detailed study will often reveal evidence of an active process. After about two weeks there is the variably explosive outbreak of a new disease, characterized by arthritis, fever and carditis in various combinations. These disorders are not the result of dissemination and focalization in the affected tissues of streptococci from the nasopharynx, nor is there anatomic evidence of true suppuration. This phase of hemolytic streptococcus disease has become known as the period of late nonsuppurative complications. Details as to fundamental mechanisms involved in the pathogenesis of these disorders have been lacking.

The fact that rheumatic fever rarely occurs in children less than 3 years old, although streptococcus disease is common in that age group, suggests that initial infections by these organisms may be incapable of producing rheumatic fever. It is therefore possible that repeated infection by group A streptococci may be essential for the establishment of the rheumatic state.

Evidence supporting this point of view and derived from bacteriologic and clinical investigation has been presented by the author and his associates (3). Murphy and Swift (5), in a brilliant study, used as an experimental tool multiple serial dermal infections of the rabbit with strains of different types of group A streptococci. Five to 10 infections over a year or more were often followed by sickening of the animal and development of a new disease not associated with the dissemination of organisms from the local lesion. Anatomic study of the tissues of these animals revealed lesions indistinguishable from those seen in fatal rheumatic fever in human beings. This work was subsequently repeated and confirmed by others.

On the basis of this evidence it is possible to make a strong case for the essential role of repeated infection by group A hemolytic streptococci in the causation of rheumatic fever. It is not possible to define with assurance the mechanisms by which such infections produce the nonsuppurative, poststreptococcic disorders. The suggestion was made early in the century that some type of immunologic reaction of an allergic nature might be responsible. The recent emphasis of the fact that widespread tissue and vascular lesions occur during the height of the allergic reaction in human beings and experimental animals sensitized to various substances has reawakened great interest in such mechanisms in the pathogenesis of poststreptococcic disorders.

It is now clear that an immunologic reaction, presumably the result of the interaction of an antigen and an antibody in the tissues, often will result in the production of lesions that are in some respects like those seen in rheumatic fever. It is difficult to go beyond this simple observation and to attempt to define fully the experimental or the human disease. Consequently, many investigators turned to a study of circulating antibodies reacting with various fractions and products of group A streptococci in the hope that the presence of one in excessively great concentrations

in the serum of rheumatic individuals might provide a clue to the nature of the process and to the identity of the possible sensitizing antigen of the hemolytic streptococcus responsible for development of the rheumatic state.

These investigations demonstrated that an individual infected by group A hemolytic streptococci who was to develop a post-streptococcic nonsuppurative complication formed, on the average, more of these antibodies in his serum than did the individual who did not develop such a complication. Three possible explanations for this phenomenon have been suggested. Frequently repeated infection may have conditioned the antibody-forming apparatus to produce excessive amounts of immune substances, persons susceptible to the development of rheumatic fever after streptococcus infection may have been inherently capable of forming more antibody, or an excessive amount of antigen may have been liberated by the streptococci during the infection.

It seems quite certain that group A hemolytic streptococci are etiologically responsible for rheumatic fever. Multiple reinfection by different strains or types of these organisms is probably essential for development of the disease.

Incomplete but strongly suggestive evidence indicates that an inappropriate immunologic process, leading to sensitization to some fraction or product of group A streptococci, is responsible for the tissue damage. It is not possible at present to determine which, if any, of the three hypotheses explains excessive antibody production by rheumatic patients or whether this phenomenon is ultimately concerned in the pathogenesis of the disease. There is no hint as to what fraction or product of group A streptococci is directly involved in sensitization or the nature of the abnormal processes by which aberrant immunologic reactions produce tissue damage. The recent discovery that adrenal steroids will modify the clinical course of rheumatic fever has failed to cast additional light on the fundamental mechanisms of the disease.

Hemolytic Streptococcus Respiratory Infection

Studies of the natural history of group A hemolytic streptococcus respiratory infections have been of considerable importance

in elucidating the pathogenesis of rheumatic fever. Clinical recognition of these disorders is essential if they are to be identified and treated adequately with antimicrobial agents which can reduce the frequency of rheumatic fever as a complication.

This topic is beyond the scope of this discussion. The work of Powers (6) and his associates, and of the author (7), has demonstrated a striking change with advancing age in the clinical and immunologic pattern of response by children infected by group A streptococci. An important feature of these studies has been the demonstration that rheumatic fever is an exceedingly rare sequel to streptococcus infection before age 4. Furthermore, prediction of the etiology of acute respiratory illness in young children is virtually impossible on the basis of the usual clinical signs associated with streptococcus sore throat. Fortunately, this is not the case in the age groups in which rheumatic fever is most likely to develop. These children often have the characteristic syndrome of exudative tonsillitis and pharyngitis which may be recognized easily, permitting the institution of appropriate antimicrobial therapy.

Epidemiology

The epidemiology of rheumatic fever is that of infections with hemolytic streptococci. Disease caused by these organisms is spread from one person to another. Large numbers of healthy carriers exist in the population and are especially numerous among children. Immunologic study indicates that nearly all of these carriers have had overlooked or inapparent streptococcus respiratory infection; it is believed that most streptococcus infection is of this type. This is to be expected, since many of these illnesses are mild and do not come under the care of a physician or may not even be associated with clinical symptoms. Difficulties of diagnosis in the absence of bacteriologic control also make recognition of the etiologic agent unlikely, particularly in young children, even though a physician is in attendance. Recognized cases of streptococcus respiratory disease are possible sources of infection but are certainly much less important than unsuspected carriers.

This huge reservoir of potential transmitters suggests that streptococcus respiratory disease is extremely common, and this is

indeed the case. Immunologic investigation revealed that, in almost 80% of a group of children 5–15 years of age, there was definite evidence of past contact with hemolytic streptococci capable of stimulating the production of antistreptolysin O. Not only does hemolytic streptococcus infection occur at least once in most children, but there is considerable evidence to indicate that reinfection is common. In a group of children studied by the author, recognizable reinfection by these organisms occurred in about 50% each year.

First attacks of rheumatic fever occur most frequently between the ages of 5 and 9. This is undoubtedly related to the greater exposure of this age group to streptococci, since young and middle-aged adults have the same susceptibility to the disease, after hemolytic streptococcus infection, as do young children. At all susceptible ages, approximately 3% of such respiratory infections are complicated by frank rheumatic fever.

The greatest risk to the rheumatic patient is contact with young children. This is a fact of considerable importance when planning chemoprophylactic regimes.

There are striking geographic variations in the incidence of rheumatic fever in the United States. The disease occurs most frequently in a rather narrow belt running north and south on each side of the Rocky Mountains, in broader areas around the Great Lakes and in the northeastern states. It is comparatively uncommon in the South and Southwest. Experience in the armed forces during World War II indicates that hemolytic streptococcus infection is endemic in these same areas. No satisfactory explanation of these facts has been proposed. It is generally not profitable to recommend that rheumatic patients move to low incidence areas since only incomplete protection against streptococcus infection and recurrence of rheumatic fever is afforded. Meticulous care and use of prophylactic regimes would usually be essential in any section of the country.

Rheumatic fever also is common in sections of large cities in which the economic level is low and standards of living are poor. Overcrowding of dwellings appears to be an important factor in creating this situation. It is more than probable that such environments foster the spread of hemolytic streptococcus infection.

There is considerable evidence which suggests that rheumatic

fever occurs more frequently in certain families than in others. Whether this is due to a genetically transmitted predisposition to the disease has not been determined. It is possible that families showing high incidence have simply perpetuated an environment favorable to the hemolytic streptococcus.

There has been a steady decline in the severity and, probably, in the frequency of occurrence of rheumatic fever in the last 20 years. It is not known why this has happened, but the effects of the widespread use of penicillin and other potent antimicrobial agents must be responsible in part. These drugs may have decreased the dissemination of streptococci by suppressing the acute disease quickly and eradicating the carrier state. Many attacks of rheumatic fever also have been aborted by treatment of the streptococcus infection.

The author predicts that the continuing barrage of antibiotics given for all types of respiratory infection may eventually eliminate the hemolytic streptococcus as a significant cause of illness in those segments of the population that receive complete medical care. Rheumatic fever presumably will disappear among these people. It is probable that rheumatic valvular heart disease will be uncommon in children who grow up under optimal circumstances during the next 20 years.

NATURAL HISTORY

The natural history of rheumatic fever may be considered profitably under two divisions—the acute and the late phases. Perhaps the most valuable of the investigations of rheumatic fever, from the clinical point of view, have been those of Bland and Jones (8). The disease which they studied and described 20 years ago was a much more violent process than the rheumatic fever of today. It is not known whether this diminishing severity will be associated with a decline in frequency of valvular heart disease. The author, in the preparation of this discussion, has drawn heavily on the papers describing these investigations. In addition, a large amount of information about rheumatic fever in young adults has become available as the result of many studies in the armed forces during World War II.

Acute Phase

The acute phase of rheumatic fever may be considered as the period from onset of the illness to establishment of a quiescent state. The duration is usually two to six months. It may be described by restating, with modifications, the well known criteria of Jones for diagnosis of the disease. These have been divided into major and minor manifestations.

Major manifestations.—1. *Carditis.*—Involvement of the heart is a commonplace in rheumatic fever. Its apparent frequency depends entirely upon the criteria used for its recognition and the duration of follow-up of the patient. During the acute illness systolic murmurs may appear over the heart, usually at the apex. Their interpretation is always difficult. Often it is impossible to determine, especially in children, whether such a murmur in this area is indicative of carditis. When apical systolic murmurs persist and become louder, one may assume that some degree of mitral regurgitation is present. Signs indicating mitral stenosis and aortic regurgitation and stenosis appear much later, after the disease has ameliorated or become quiescent, and are not often helpful in the early diagnosis of carditis.

Cardiac enlargement, when definite, strongly suggests that carditis is present. Usually serial study demonstrating an increase (or decrease) in the size of the cardiac silhouette is required because the standards of normal heart size, particularly in children, are inadequate. Inspection of a single film will not permit a definite statement regarding cardiac enlargement, unless it is great.

A friction rub indicating pericarditis is positive evidence of cardiac involvement in rheumatic fever. Fluid often accumulates in the pericardium but is difficult to detect in the absence of a rub unless the amount is very large. Pericarditis is extremely uncommon in adult rheumatic fever; it can be demonstrated in less than 2% of all cases, regardless of severity.

Heart failure, when it occurs in a child or young adult with probable rheumatic fever or with established rheumatic valvular heart disease, is reliable evidence that carditis is present. Not infrequently the appearance of signs of cardiac insufficiency is the first and only clinical indication of recrudescence of rheumatic activity.

Abnormalities in the electrocardiogram, discussed later, are often the only evidence of carditis obtained during the acute phase of rheumatic fever. They may be utilized as a satisfactory index of the presence of this manifestation of the disease if the tracing is conservatively interpreted.

Clinical (usually an apical systolic murmur) and laboratory (abnormal electrocardiogram) evidence of carditis was discovered in 40–70% of young adults with definite arthritic rheumatic fever in the army during the last war. Variations in incidence from one hospital to another resulted from application of different criteria for the detection of cardiac abnormalities. The frequency of occurrence of this manifestation in children would doubtless be approximately the same as in these young adults if the disorder were of comparable severity. Clinical and laboratory signs of carditis are extremely difficult to obtain in mild and atypical forms of rheumatic fever. It is precisely in these cases that the discovery of such evidence is most important diagnostically.

2. *Arthritis.*—Migratory arthritis, often involving several joints asymmetrically, is characteristic of rheumatic fever. The joints may be greatly swollen and hot and exquisitely painful in severe cases. In these circumstances, rather sharply circumscribed patches of erythema over the affected joints is the rule. The knees, ankles and feet are usually involved first and most violently. The trauma of weight bearing probably predisposes these joints to arthritis. Disturbances in the upper extremities, shoulders and hip are less common. The spine and temporomandibular joints are almost never affected. The distribution of arthritis may be of help in differential diagnosis. Objective evidence of arthritis may not be obtained in many cases of rheumatic fever, although arthralgia may be a major complaint.

It is not possible to determine the true frequency with which arthritis occurs because no absolute criteria for the recognition of rheumatic fever are available. An investigation which begins with the initiating hemolytic streptococcus infection always discloses a considerable number of nonarthritic cases. In the author's experience, 30–50% are in this category. Ancillary evidence which indicates that this estimate of frequency is approximately correct is the well known observation that no history of rheumatic fever is obtained in about half of all adolescents who have

rheumatic valvular heart disease. It is evident that the rheumatic process in most of these was nonarthritic, since arthritis is such a dramatic and painful disorder that it is not often likely to be overlooked or forgotten.

If a study begins with a search for rheumatic fever in sick children and young adults, the estimate of frequency of arthritis will be quite different, since it is joint pain that often calls attention to the fact that the individual is ill and dictates the need for medical attention. In many instances the diagnosis will not be suggested to the physician if arthritis is absent. Ninety-eight per cent of all men admitted to rheumatic fever centers of the U. S. Army during World War II, and 81% of the patients of Bland and Jones, had arthritis or arthralgia. On the other hand, the author has records of 30 children of whom only 17 (56%) had arthritis, although all had definite rheumatic fever, usually with carditis.

It is possible that nonarthritic rheumatic fever has become more common in recent years as the severity of the disease has diminished. Certainly it is often overlooked. Its recognition with the available clinical tools is enormously difficult and new diagnostic methods are urgently needed.

3. *Chorea.*—There can be no doubt that the central nervous system is involved in some patients with rheumatic fever and Sydenham's chorea may result. Twenty-five years ago, 50% of rheumatic patients exhibited this symptom, but it has now become much less common and occurs in less than 20% in California today. It is virtually unknown in adults with rheumatic fever.

"Pure" chorea in which none of the usual clinical manifestations of rheumatic fever are evident is, in many respects, a different disease. Fever is absent, the erythrocyte sedimentation rate is often normal and C-reactive protein is usually not present in the serum. Rheumatic valvular heart disease subsequently develops in only 5% of these cases.

Kagan has ably reviewed the arguments in favor of the separation of pure from rheumatic chorea, but 50 years of investigation have failed to define accurately the relationships between them (9).

A study of antistreptococcic antibody patterns in the two dis-

orders might clarify the situation; the author is not aware of any published investigation of this important matter. He has studied cases of chorea without evident rheumatic manifestations in which the serum levels of antistreptolysin O were high and has no records of this disease with titers less than 100 units per ml. It is impossible to exclude an association with rheumatic fever in any of these cases.

4. *Subcutaneous nodules and dermal lesions.*—Subcutaneous nodules over the tendon sheaths at the elbows, knees, ankles, fingers and occiput may appear during protracted severe rheumatic fever. They are rarely seen since the disease has become milder and are unknown in adults. Their diagnostic importance seems to have been overemphasized, since very similar lesions appear in rheumatoid arthritis, a disorder which may be readily confused with rheumatic fever early in its course.

Erythema marginatum is the characteristic dermal lesion of rheumatic fever. Two per cent of young adults and 8% of children exhibit this lesion. It occurs most frequently in chronic active cases.

Another dermal lesion, erythema nodosum, is frequently a late nonsuppurative complication of hemolytic streptococcus infection although it is also associated with other diseases including tuberculosis, coccidiodomycosis and drug reactions. Although fever and arthritis are common accompaniments of the disorder, which may be protracted and relapsing, it does not seem to be related to rheumatic fever, and valvular heart disease is not a sequel (10).

MINOR MANIFESTATIONS.—This term, used to describe certain aspects of the acute phase of rheumatic fever, is unsatisfactory, because many are striking and disabling disturbances. Fever is the most common and least specific. Nosebleeds occur in about a fourth of rheumatic children but are rare in adults. Precordial pain is a frequent complaint during severe rheumatic fever at all ages, often in the absence of convincing evidence of pericarditis. Abdominal pain occurs chiefly in children, and it is well known that the onset of acute rheumatic fever may be confused with an intra-abdominal emergency. Pneumonitis is an integral part of the rheumatic process. It may be demonstrated by roentgen study but only occasionally by clinical examination in a few of the more severely ill patients. The author doubts that rheumatic

pneumonitis occurs as an isolated disturbance in the absence of an extensive and readily recognizable episode of rheumatic fever.

Certain abnormalities in laboratory tests have been included in the minor manifestations of rheumatic fever. These include anemia, leukocytosis and reactions indicating the presence of inflammation. They are all completely nonspecific and will be discussed later.

Late Phase

A complete description of the natural history of rheumatic fever after the apparent subsidence of the acute phase is impossible today. It has long been recognized that the disease has an extraordinary tendency to recur, usually as a result of infection by the hemolytic streptococcus. Quiescent periods generally have been regarded as intervals of complete resolution of the inflammatory process, although it was known that activity could continue at a very low level for long periods. Microscopic study of auricular appendages removed during mitral commissurotomy has revealed typical Aschoff bodies and other signs of active rheumatic fever in about 30% of persons coming to operation (11). Many of these patients had been studied carefully, and no clinical evidence of rheumatic activity had been obtained. The antistreptolysin O levels were often very low, indicating that these individuals were far removed in time from the acute illness.

These observations demonstrate that any attempt to determine the termination of active rheumatic fever by clinical study will be fruitless. They also probably explain certain examples of apparent rheumatic recurrence in the absence of demonstrable streptococcus infection, since it is well known that recrudescences may be precipitated by various stresses, such as surgical operation, when complete quiescence has not been attained. A rational basis for the delayed development of valvular heart disease is also offered by these studies.

Rheumatic fever, then, can be defined as a disease whose onset may often but not always be recognized by clinical study. The termination of the inflammatory processes can be only a matter for speculation in the absence of anatomic examination.

The most important aspects of the late phase concern themselves with recurrence and the development of valvular heart

disease, congestive failure and subacute bacterial endocarditis.

1. *Recurrence.*—Rheumatic fever has a great tendency to recur if protection against hemolytic streptococcus infection is not provided. In patients who have not attained complete resolution of the rheumatic process, recrudescences may result from stress in the absence of contact with streptococci. These patients will have all the clinical manifestations of true recurrences.

Bland and Jones recognized recurrences in one in five of their patients in the five years after the first attack and in one in 10 during the next five years. Unrecognized episodes of activity probably occurred. For these reasons, patients seen for the first time with active rheumatic fever often present a history of similar episodes and may have established rheumatic heart disease.

2. *Valvular heart disease.*—Bland and Jones defined the consequences of rheumatic fever in 1,000 patients followed 20 years after the initial episode (8). They may be summarized here. At the end of the period of observation, a third had no evidence of disease, a third had rheumatic heart disease and a third were dead. Eighty per cent of those who died did so as the result of congestive failure or active rheumatic fever. Ten per cent had bacterial endocarditis; the rest succumbed to miscellaneous conditions.

Approximately one third of those with valvular heart disease had no or slight limitation of activity, and another third had moderately restricted activity. Less than 2% were in severe difficulty. These were much more optimistic results than were generally believed to be attainable in children with rheumatic fever. They can doubtless be vastly improved by the use of chemoprophylactic regimes during the period of greatest risk of recurrence.

The development of heart disease with reference to the valves involved and other details will not be considered, but two features deserve special comment. One pertains to the delayed appearance of the signs of valvular damage. With each five year follow-up period the number of patients with clinical evidence of valvular deformity increased. It is well known that mitral stenosis evolves slowly and that several years are often required for this lesion to become fully evident clinically. It has not been so well appreciated that as many as 24% of patients who escape apparent valve disease after an acute attack of rheumatic fever will develop

signs of heart disease during the next 10 years. Even more striking is the fact that an additional 20% will acquire valvular disease in the next decade. Only a small proportion of these patients will exhibit clinical evidence of rheumatic activity during this period. The explanation for these phenomena may well lie in the observations that rheumatic activity may persist at the tissue level when it is not demonstrable by any clinical techniques.

Another important contribution of Bland and Jones has been the finding that rheumatic valvular heart disease may lessen in intensity or disappear with the passage of time. This does not occur when aortic insufficiency or mitral stenosis is firmly established. As many as 15% of patients with loud apical systolic murmurs or faint diastolic murmurs at apex and base had a complete regression of signs and a return of the heart to normal size if it was previously enlarged. An additional 15% displayed lessened intensity of clinical signs of valvular disease.

All of this information demonstrates that the physician should be guarded in his prognosis after an attack of rheumatic fever. No prediction as to the extent of valvular damage should be made for one to two years. After this time the over-all condition can be expected to be good, and many patients will have an improved cardiac status after a few years, but some will be worse even though no recurrence takes place.

3. *Congestive heart failure.*—The principal cause of death in rheumatic heart disease is congestive heart failure. A remarkable feature of the disorder is the frequently long latent period between the appearance of well defined signs of valvular disease and the onset of cardiac insufficiency. During this time the patient may be quite well or have no more than slight dyspnea.

Heart failure may be precipitated by a recurrence of active rheumatic fever, often without other manifestations of the disease. This is most likely when cardiac insufficiency supervenes in children and young adults with rheumatic heart disease, but it should be considered in older persons as well, especially if no other predisposing events have occurred. Most often heart failure results from mechanical disturbances within the heart, usually associated with mitral stenosis, with or without insufficiency, or with aortic stenosis. Pure rheumatic aortic insufficiency is usually very well borne.

The events occurring during the latent period which lead to the appearance of heart failure are not clear. Sometimes it is precipitated by the onset of auricular fibrillation or flutter, or by the increased work of pregnancy or hard physical labor. More often there has probably been progression of the valvular deformity with impairment of cardiac efficiency. In mitral stenosis, pulmonary resistance also may be increased gradually by changes in the pulmonary vascular bed resulting from long-continued pulmonary hypertension, with eventual decompensation of the right ventricle.

Once established, cardiac insufficiency persists, although response to appropriate treatment is often good for a time. A complete regression of all evidence of heart failure, permitting withdrawal of specific therapy, should suggest strongly that the condition was precipitated by an episode of acute rheumatic fever which supervened and subsided without presenting obvious signs.

Very often, release of obstruction to the flow of blood within the heart by intracardiac surgery is required if patients with rheumatic heart disease are to be benefited. The development and applications of these dramatic techniques are beyond the scope of this discussion.

It may be well to describe a curious syndrome that sometimes follows surgery of the heart in rheumatic patients. Usually the recovery from operation is uneventful, but convalescence is sometimes interrupted after a few weeks by the explosive appearance of fever and pain in the chest which regresses, often within a few days, without specific therapy. Several relapses may be observed in the next few months. The pathogenesis of this disorder is unknown, although it is thought by many to be rheumatic recrudescence precipitated by surgery. Its course is not like that of rheumatic fever and its occurrence does not correlate well with the presence of Aschoff bodies in the excised auricular appendage. It probably should be regarded as a postoperative complication of unknown cause for the moment (12).

4. *Bacterial endocarditis.*—Bacterial infection of heart valves damaged by rheumatic fever is well known. It is not very common, since only 4.5% of 653 patients studied by Bland and Jones in a 20 year period had such an infection (8).

Recovery is now the rule when subacute bacterial endocarditis

is treated adequately with antibiotics. The most effective drug is penicillin, which usually should be combined with streptomycin. Many patients have serious deterioration in cardiac status after the infection has been eradicated. For this reason there has been great interest in antibiotic prophylaxis accompanying surgical operations, especially tooth extractions, which often provide portals of entry for the infectious agent. No satisfactory prophylactic regime has been defined, although many are employed. The comprehensive review of this important disease by Finland is recommended for details of prevention and management (13).

RECOGNITION

The recognition of typical rheumatic fever is not difficult. The appearance of arthritis, myocarditis, pericarditis, dermatitis, subcutaneous nodules and chorea in various combinations in individuals with fever and the laboratory signs of inflammation make diagnosis simple. Confusion with other members of the group of collagen diseases is possible, particularly in young women. A history of a similar illness or physical evidence of rheumatic valvular heart disease enhances the possibility that the disease is rheumatic fever. The commonly used criteria of Jones limit the diagnosis to disorders that exhibit several of these important manifestations of rheumatic fever (14). However, careful investigation of children and young adults during the poststreptococcic period reveals that rheumatic fever develops in a considerable number even when few or none of these definitive signs are present. An effort must be made to recognize such atypical cases.

No other diagnostic problem in medicine is more taxing and less rewarding. Often a diagnosis cannot be made even after exhaustive study and the sick person must be observed over a long period with serial physical, electrocardiographic, roentgen and laboratory examinations. It is always unwise to stigmatize an individual as rheumatic unless the diagnosis is definite, because of the emotional reaction, accompanied by extreme anxiety, which often develops in the patient and his family.

It is clear that rheumatic fever must always be considered in patients who present any of the aforementioned characteristic signs. It must also be included in differential diagnosis of chronic

and subacute febrile illnesses in which these clearcut manifestations are absent. This is particularly important in children between the ages of 5 and 15. The disease process in these cases is so ill defined that clinical diagnosis becomes impossible, and resort to laboratory procedures is essential although it often is unprofitable. Unfortunately, no specific test for rheumatic fever is available. Laboratory diagnosis must be by exclusion, using indirect methods. The most useful procedures involve the use of the electrocardiogram, x-ray and hematologic procedures, tests that demonstrate the presence of inflammation and those that reflect the presence or absence of recent hemolytic streptococcus infection.

THE ELECTROCARDIOGRAM.—Abnormalities in the electrocardiogram are common in patients with rheumatic fever (15). They occur with increasing frequency as the disease becomes more severe. Significant alterations in the tracing are least likely to be discovered in patients whose diagnosis is doubtful. Nevertheless, an important clue to the nature of an illness may be obtained by the demonstration of a definite increase in the atrioventricular conduction time or alterations in the T waves.

Serial electrocardiograms will increase the frequency of demonstration of abnormalities since they are often evanescent. Questionable variations from normal may be clarified if changes occur with time. A serious error in the study of difficult cases of possible rheumatic fever is often made by failing to obtain several electrocardiograms. More important is the tendency to over-read the electrocardiogram. Only too frequently patients with vague illnesses have been stigmatized as rheumatic and undergone needless and elaborate therapy because of minor variations in the electrocardiogram which were not beyond the range of normal. The P–R interval should not be regarded as abnormal unless it is greater than 0.20 seconds or unless it shortens or lengthens on serial tracings by more than 0.04 seconds.

Lengthening of the Q–T interval has been proposed as another index of rheumatic activity. The measurement of this value depends on the use of a formula which is intended to correct for the effect of the heart rate. The author believes that measurement of the Q–T segment should not be used as a criterion for determining the presence or absence of carditis.

T wave abnormalities appear to be more frequent in adult than in childhood rheumatic fever unless pericarditis is present. Definite inversion of these waves in leads I and II or in the precordial leads strongly suggests myocarditis. Various degrees of flattening, even if changes occur in serial records, are extremely difficult to interpret.

X-RAY.—Roentgen examination of the heart and lungs is of little value in the study of patients with possible rheumatic fever since the patient with the difficult case is most often only moderately ill, and no abnormalities can be detected. In the severe forms of the disease striking changes in contour of the heart will be observed, with increase in size often due to pericardial effusion. Pneumonitis also may be demonstrated in such cases. A base line roentgen study of the chest should be obtained in all cases, even though it may be unrewarding diagnostically, as it will be important in the follow-up investigation of the case if rheumatic fever is present. It also assists in the exclusion of other disorders.

HEMATOLOGIC PROCEDURES.—Anemia and leukocytosis are frequent manifestations of rheumatic fever. Their presence rarely has diagnostic value since both occur in many other conditions, but their serial measurement may be of importance in estimating the progress of treatment.

TESTS INDICATING PRESENCE OF INFLAMMATION.—Inflammation (or malignancy) of any sort may stimulate production by the body of certain proteins in the serum that either are not demonstrable in health or normally are present in much smaller amounts. Several of these have been estimated directly or indirectly and the results used in the study of rheumatic fever. It should be emphasized that the tests to be described are measurements of entirely nonspecific phenomena and have no differential diagnostic value. They are often called "acute phase reactions." Abnormal results for any of the tests may be obtained in the presence of almost any sort of infection, either bacterial or viral, malignancy or collagen disease, including rheumatic fever. They may be useful at times in determining whether any disease at all is present and are important in evaluating the progress of the illness under treatment.

The rate of sedimentation of erythrocytes, which is related to the amounts of fibrinogen and globulin in the serum, has been

the most widely applied of these procedures. Several methods have been described. The author strongly recommends the use of the Westergren technique uncorrected for anemia. The long (200 mm.) tube permits a much greater differential between abnormal rates than do the short tubes of other procedures. This is of distinct value in the serial study of the patient with rheumatic fever.

A protein, termed the C-reactive protein, appears in the blood in the presence of inflammation. It forms a precipitate in the presence of a carbohydrate extracted from pneumococcus. When purified and injected into rabbits, it stimulates the production of an antibody* which may be used to detect and crudely quantitate the amount of C-reactive protein in the serum of patients. Several investigators have shown a close correlation between rheumatic activity and its presence in the serum. The only exception to this generalization is in chorea, in which the result of the test is often negative (16).

Absence of this protein during the diagnostic examination would exclude active rheumatic fever even though other values, such as the erythrocyte sedimentation rate, were abnormal. Its persistence during treatment has been accepted as evidence of continuing activity requiring intensive management and its disappearance is considered an indication of quiescence. C-reactive protein usually disappears from the blood before the erythrocyte sedimentation rate has returned to normal.

Other substances, including mucoproteins, heat-labile antihyaluronidase inhibitor and the proteins responsible for the Weltman band phenomenon and for the diphenylamine reaction, also appear or increase in inflammation. All have been utilized in the diagnosis and treatment of rheumatic fever, but clinical experience with none except the estimation of mucoproteins (17) is extensive, and laboratory procedures for those are not widely available. It is unlikely that any will supplant the estimation of erythrocyte sedimentation rate and the more recently introduced estimation of C-reactive protein in the diagnosis of this disease.

The difficulty of determining the duration of rheumatic activity has been indicated. It will be evident that no test can be

* Manufactured by Schieffelin & Co., New York.

calibrated to determine this time precisely. The procedures described can only be used as general guides to the duration of active treatment. The patient's welfare must not be compromised by an overdependence on the laboratory, in regard either to diagnosis or to treatment.

TESTS INDICATING RECENT STREPTOCOCCUS INFECTION.—In the first section we described the intimate relationship between group A hemolytic streptococcus infection and rheumatic fever. As a consequence, the serum of rheumatic patients regularly contains considerable amounts of a variety of antibodies reacting with various products and extracts of these organisms. Antistreptolysin O, antistreptokinase, antibacterial precipitating antibodies, type specific bacteriostatic antibodies, complement-fixing streptococcic nucleoproteins and streptococcic antihyaluronidase have all been demonstrated in the serum of patients with rheumatic fever in much higher concentrations, on the average, than in healthy persons.

It was natural that attempts should be made to utilize the measurement of such antibodies in the diagnosis of rheumatic fever, and several have been evaluated. Only the estimation of streptolysin O may be widely performed, using a commercially available standardized antigen.* This procedure will be discussed in detail.

Streptolysin O is the oxygen-labile hemolysin produced by group A streptococci (and by some strains of groups C and G). It is freely elaborated in culture media and may be concentrated and desiccated, and is then highly stable. It must always be activated by the addition of a reducing agent which is added at the time of use or before desiccation. The latter process is applied in the commercial preparation. A standard amount of the active lysin is mixed with suitable dilutions of serum. Neutralization of the toxin by antistreptolysin is demonstrated by addition of a suspension of erythrocytes after the serum and toxin have been incubated together. The result is expressed in units.

The measurement of antistreptolysin O simply indicates the degree of probability that the patient has had a recent hemolytic streptococcus infection. There is no known specific relationship

* Manufactured by Difco Laboratories, Detroit.

between the streptolysin O–antistreptolysin O system and the pathogenesis or course of rheumatic fever.

Since this disease begins two to four weeks after the onset of the initiating streptococcus infection, the antibody response is usually nearly or actually maximal at this time and the antibody levels tend to be well maintained for several weeks. For this reason it is impossible to utilize the familiar rise in antibody titer for the demonstration of a preceding streptococcus infection.

To use a measurement of antibody as a diagnostic tool when

TABLE 1.—ANTISTREPTOLYSIN O TITERS IN SERUM OF HEALTHY PERSONS OF VARIOUS AGES AND IN RHEUMATIC FEVER

SERUM ANTISTREPTOLYSIN O TITER, UNITS*/ML	AGE							
	5–12		18–30		40–60		In Early Active Rheumatic Fever	
	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %
12 or less	30	22.6	23	19.4	83	62.4	0	0.0
50	14	33.1	40	52.5	27	82.7	0	0.0
100	10	40.4	10	60.8	9	89.5	3	3.6
125	12	49.6	19	76.6	7	94.7	5	8.6
166	22	66.2	17	90.9	3	97.1	19	29.4
250	10	73.7	5	95.0	1	97.8	16	46.7
333	13	83.5	3	97.5	3	100.00	11	58.7
500	9	90.2	3	100.0	—	—	12	71.7
625	6	94.8	—	—	—	—	11	83.7
833	4	97.8	—	—	—	—	9	93.5
1,250	3	100.0	—	—	—	—	6	100.0
Total	133	—	120	—	133	—	92	—

* The unit is the same size as that in commercially available streptolysin O reagent.

only a single convalescent serum is available, a statement of the antibody pattern of the healthy population and of diseased individuals is required. Such information about antistreptolysin O is presented in Table 1. The data demonstrate that measurement of antistreptolysin O is most useful for the *exclusion* of rheumatic fever. Titers were 100 units or more in every case of early active disease and in only 12% were less than 166 units. While occasional exceptions to this observation have been reported, it is evident that antibody titers of 50 units or less are virtually incompatible with the early stage of rheumatic fever.

This information is of great importance since inspection of the table reveals that about one third of healthy children in the age group in which rheumatic fever is most common, about one half of young adults and four fifths of older persons may be expected to have serum antistreptolysin O titers in the low range. Rheumatic fever is readily eliminated from diagnostic consideration in these individuals by measurement of antistreptolysin O content of the serum.

This procedure is unsatisfactory for the positive diagnosis of rheumatic fever. Interpretation of higher serum titers is difficult because there is much overlapping of the levels in healthy and diseased persons, especially in childhood. Concentrations of 500 units or more of serum antistreptolysin are rarely discovered in individuals who have not had a recent hemolytic streptococcus infection. This information will often suggest that an illness is rheumatic fever but it can never be employed as a conclusive diagnostic criterion.

The concentration of antistreptolysin O in the serum falls slowly after onset of acute rheumatic fever. This decline is not correlated with the activity of the disease and the test is of no value in the evaluation of the course of the illness. In patients unprotected by chemoprophylaxis, a recrudescence is often accompanied by a rise in antistreptolysin O, indicating that an intercurrent hemolytic streptococcus infection is responsible for the activation of the disease. Various stressful situations unrelated to the streptococcus infection will cause flare-ups of disease in persons with active rheumatic fever. These are not associated with increases in antibody.

TREATMENT

Rest and Other General Measures

Restriction of activity has been the mainstay of treatment of rheumatic fever for many years. There is no disagreement about the fact that the rheumatic patient should rest in bed during the early active stage of the illness when malaise and joint discomfort are severe and the danger of heart failure is greatest. This phase usually subsides rapidly when anti-inflammatory drugs are administered in effective amounts. Within two to three weeks there

is often almost complete disappearance of clinical evidence of active disease although minor degrees of malaise and abnormal results of laboratory tests may persist for a much longer period.

In the past it was the custom to maintain a regimen of strict bed rest throughout this period and until all laboratory evidence of active disease had disappeared. Fantastic degrees of inactivity were often ordered, the sick person being forbidden to feed or wash himself or even to sit up in bed. These restrictions were imposed because it was thought that they would provide rest for the heart and that this would reduce the subsequent incidence of valvular heart disease. It should be emphasized that there was no real evidence that this was so.

Recently, there has been a pronounced trend toward the liberalization of activity for patients with all forms of heart disease. It has been realized that rest is a relative term and that confinement to bed is not necessarily synonymous with it. Rest means maximal comfort, physically and emotionally, and ceases to be effective when the individual is no longer at ease in his environment. Prolonged over-restriction of activity is associated with restlessness and may well increase physical and psychic effort. When accompanied by too frequent clinical, electrocardiographic and laboratory examinations, particularly in an atmosphere of intense family concern, anxiety neurosis is likely to develop.

Careful studies in the armed forces during World War II failed to demonstrate any deleterious effect on the course of acute rheumatic fever when patients with this disease were permitted to have bathroom privileges and to sit in a chair by the bed as soon as the major manifestations had been controlled with anti-inflammatory drugs. Later these men were allowed to be ambulant about the wards within the limits imposed by fatigue. Recovery occurred in the expected length of time and there was no increase in incidence of valvular heart disease.

The optimal regime is that which attains a maximum of physical and emotional rest over a period of several months without establishing a neurotic behavior pattern. This usually is best accomplished by instituting complete rest in bed until anti-inflammatory drugs have exerted their full effect. This will require one to two weeks. If the clinical response is satisfactory, bathroom privileges should be permitted. If this program is accepted well,

it may be continued until all clinical signs of disease activity have disappeared. If it is not, and restlessness becomes a problem, a bed and chair routine should be instituted.

After four to eight weeks, most patients feel quite well and may be allowed to increase their activity around the home or hospital, avoiding fatigue. Two to four weeks after the laboratory evidences of activity have disappeared, a program of rehabilitation designed to return the patient rapidly to full activity should be instituted. This usually can be accomplished within four to six months after the initiation of treatment.

If the home situation is appropriate there is no reason why the convalescent should not be treated there after the early acute phase of the disease has passed. However, this is often not possible in that segment of the population in which rheumatic fever occurs most frequently. Special rheumatic fever hospitals are most desirable for treatment of patients in this group. The general hospital does not supply a satisfactory emotional climate for the necessary protracted care of children with rheumatic fever, and it is far from ideal for adults.

Clinical examinations, especially of the heart, should not be performed too frequently in patients progressing favorably, as the findings contribute little to management and may increase the anxiety of patient and family. Laboratory observations may be made at monthly intervals after the diagnosis is established and the therapeutic regime well under way.

Two principal problems arise in the management of the rheumatic subject. One relates to the patient whose course under therapy is satisfactory but in whom abnormalities in certain laboratory findings remain after several months of limitation of activity. A moderate elevation of the erythrocyte sedimentation rate or prolongation of the P–R interval in the electrocardiogram are the usual disturbing features of these cases. It is in this situation that estimation of the amount of C-reactive protein in the serum is of greatest value. Restriction of activity is in order until it disappears. Its absence indicates that the disease is approaching quiescence and rehabilitation may be begun cautiously, even though the results of other laboratory tests are abnormal. If the C-reactive protein cannot be measured, these other laboratory

findings should be disregarded after a moderate prolongation of rest, since they may persist indefinitely.

A second troublesome problem is presented by the situation, almost unknown in adults but not uncommon in children, of continuing low grade rheumatic activity. These patients show definite clinical evidence of a continuing disease process manifesting itself by low grade fever, irritability, easy fatigability, anemia, failure to gain weight and sometimes evidence of carditis and arthritis. Certain patients exhibit a polycyclic course with remissions and exacerbations. Arthralgia alone should not be overemphasized, as residual joint pain persisting for many months after termination of the active phase is a commonplace, especially in adults.

There is no fully satisfactory regimen for the management of chronic rheumatic activity. Anti-inflammatory agents will not control it, but they should be continued, because their withdrawal may lead to serious exacerbations. Prolonged rest under optimal conditions for the promotion of emotional and physical well-being is required. This can often be obtained only in a convalescent home.

Ancillary general measures are of little importance in the management of rheumatic fever. The diet should be rich in protein and vitamin C. The patient should be well nourished but in no circumstances should he be allowed to become obese. Sodium need not be restricted unless heart failure is present or adrenocortical steroids are to be administered. Simple sedatives may be required for brief periods to control restlessness.

Specific Anti-Inflammatory Drugs

Fischel has stated: "an ideal therapeutic agent [for rheumatic fever] should consistently abort the manifestations of the acute illness, terminate the unknown processes which initiate and perpetuate the disease, and prevent cardiac sequelae. As yet, no drug has been found to fulfill these requisites" (18). Nevertheless, two groups of agents, salicylic acid and its derivatives and adrenocortical steroids, have a profound anti-inflammatory effect in rheumatic fever and can alter the course dramatically. In some respects these substances approximate the goals of the ideal agent.

It is a curious fact that salicylates were introduced into the

treatment of rheumatic fever more than 50 years ago and yet there is no substantial agreement among physicians as to their effect on the disease or their proper role in treatment. At one extreme it is held that they are merely anodynes and antipyretic agents, while on the other hand they are regarded as having an intimate and direct effect on the disease process. The author believes that the truth lies much nearer the latter than the former point of view and that their use is mandatory in the management of the rheumatic subject.

The more recent introduction of adrenocortical steroids in the treatment of rheumatic fever has aroused much interest. These drugs also suppress the inflammatory reaction in the tissues and terminate many or all of the clinical manifestations of the disease. It is not clear from the data presented thus far that they accomplish these effects more completely than do salicylates. A few investigators have felt that steroids, in some instances in brief courses, definitely altered the total course of the disease favorably. Others have been impressed with the immediate effects but have not observed any definite shortening of the illness or improvement as to prognosis for life or recovery without valvular heart disease. It might be supposed that the very rapid suppressive action obtained with adrenal steroids would be of great benefit in the gravely ill, especially those with heart failure. Even in these circumstances, steroid has not been proved to be superior to salicylate therapy (19, 20).

Neither of these groups of drugs appreciably shortens the basic pathologic process, and relapse will occur after their withdrawal long after apparent complete suppression of the disease. Their administration will not completely prevent the subsequent development of valvular heart disease. Whether their use ameliorates the course of these lesions is unknown. It is difficult to believe that there can be no effect whatever when their action on clinically demonstrable manifestations of the disease are considered.

Salicylic acid and its derivatives seem to remain the drugs of choice for the treatment of rheumatic fever. The numerous hazardous side actions of steroids make their use in the moderately ill patient inadvisable. On occasion, in the severely ill, their rapid suppressive action may be desired, but great caution must be ex-

ercised to prevent salt retention, particularly when carditis is present. Congestive heart failure may easily follow.

Many of the divergent opinions in regard to the value of salicylates have arisen in the past, as emphasized by Fischel (18), because they have been improperly used. The dosage or the duration of therapy, or both, has been inadequate. Usually the drug has been withdrawn after relatively brief periods of suppression of the rheumatic process, to determine whether the disease was still active. This curious custom does not have a sound rational basis and has been accompanied by serious rebound replase which has proved uncontrollable and resulted in death. Proper use of these agents involves their administration in just subtoxic amounts without rest periods or trial withdrawals throughout the period that rheumatic activity might be expected to continue. This would be an interval of at least six months in the average case.

A satisfactory regimen involves the administration on the first day of treatment of 5 Gm of aspirin in divided doses in adults, or 30 mg. per lb. in children. This amount is increased daily at a rate of 1 Gm in adults, or 0.6 Gm in children, until the first signs of salicylism are observed. These are tinnitus, deafness, headache, diarrhea, nausea and vomiting. The dose should then be reduced until the patient is again comfortable. Most rheumatics tolerate such a program well and can continue the drug for many months without discomfort.

Adrenocortical steroids may be used in two ways. One which is simple, safe and often desirable involves the administration of corticotropin as the gel intramuscularly in a dose of 40 units twice daily for three to seven days. The disease is brought under control very rapidly and patient co-operation is excellent. Salicylate therapy is begun on the second or third day as has been described, and as soon as full dosage is reached the corticotropin is withdrawn. Cortisone or hydrocortisone may be used in the same way and given by mouth, but the effect is produced a little less rapidly. These regimens take advantage of rapid steroid suppression of rheumatic activity without serious hazard unless severe carditis with heart failure is present. In the latter instance sodium intake should be sharply restricted and a mercurial diuretic administered if any evidence of congestive failure supervenes.

More conventional therapy involves the administration of

adrenal steroids over a long period. Most investigators have used courses of four to six weeks at full clinical dosage, followed by the usual period of tapering off. Hyperadrenocorticism has often been noted. There is no good evidence that these regimens offer any advantage over those described. The hazards seem too great for their regular use. Steroid therapy must not be withdrawn until salicylates are being administered in full dosage; otherwise, serious rebound relapse may occur.

There is no real evidence that salicylates or adrenal steroids have any effect on the course of Sydenham's chorea. The available information in regard to the steroids was summarized by Schwartzman (21), who collected 17 treated cases from the literature and added six of his own. He concluded that steroids were beneficial in some instances, but eight individuals completely failed to respond and the results in the others were no better than those obtained by him a few years ago from a variety of presumably inert agents.

Hemolytic Streptococcus Infection

Prevention.—The evidence summarized earlier demonstrates that rheumatic fever is a complication of hemolytic streptococcus respiratory infection. Approximately 50% of new group A streptococcus infections occurring in individuals who have had rheumatic fever will be followed by recrudescences of varying degrees of intensity.

Prevention of such infections in the rheumatic subject is mandatory and may be, in theory, accomplished in several ways. This whole subject has been extensively reviewed elsewhere (2). It was pointed out that measures designed to prevent exposure of the rheumatic patient to streptococci must fail. This is so because a large number of group A carriers exist in the childhood population and because unrecognized cases of disease caused by these organisms are extremely common. The susceptible person will be constantly at risk unless he is isolated in a streptococcus-free environment. This may be accomplished only in a special hospital. Active immunization has also been unsuccessful for technical reasons.

These facts have stimulated great interest in chemoprophylaxis.

It has been established that the continuous daily administration of a sulfonamide will prevent streptococcus infection and rheumatic recrudescences in the rheumatic subject. A summary of available experience indicates that a 93% reduction in recurrences of rheumatic fever may be expected in groups of rheumatic children receiving prophylaxis (2).

Toxic reactions have been surprisingly few, but the potential hazards of long-continued administration of sulfonamides have discouraged widespread application of this valuable technique. For this reason, penicillin prophylaxis has been explored since this agent has become cheap and plentiful. When given by mouth it is clearly effective, but the optimal regimen has not been determined. Administration twice daily of rather large amounts (200,000 units) has been utilized in most clinics, but this has made the program too costly and complicated, and patient co-operation has been unsatisfactory. Many failures have occurred during oral prophylaxis with either penicillin or sulfonamides through the neglect of patients to take the drug. It is notoriously difficult to carry out continuous therapy requiring patient participation because apathy often develops. This is particularly evident in populations of the cultural and educational level in which rheumatic fever most often appears.

An important new tool which eliminates certain of these difficulties has recently been introduced. Benzathine penicillin* is only slightly soluble in body fluids and is absorbed very slowly from a depot in muscle. Stollerman and Rusoff (22) have shown that the injection of 1,200,000 units of this material at monthly intervals effectively prevents streptococcus infection and recurrences in persons who have had rheumatic fever. The availability of this material permits the establishment of a prophylactic regimen in which no responsibility lies with the patient beyond a visit to the physician or clinic each month. This should be an extremely valuable technique in many instances.

Of great significance and importance is the exciting possibility which now exists for the long-term investigation of rheumatic fever in persons completely protected against hemolytic streptococcus infection. It has been emphasized that all of the magnifi-

* Dibenzylethylenediamine dipenicillin G.

cent earlier investigations of the natural history of this disease have been carried out in individuals many of whom had recognizable recurrences. A large number of inapparent rheumatic recrudescences must also have occurred following streptococcus infections. Some information from protected rheumatic patients has been obtained by clinics using oral prophylaxis, but their information has not been published. Now programs are being established in which monthly injections of benzathine penicillin will be administered to large numbers of rheumatic children. Positive protection against streptococcus infection can be obtained and the patients will be kept under close medical observation and control. The results of these investigations are eagerly awaited.

Nearly every investigator who has considered the problem of chemoprophylaxis of rheumatic fever has recommended a different regimen. Probably all would agree to the following principles. (1) Prophylaxis should be instituted immediately in all individuals in whom the diagnosis of rheumatic fever is certain. (2) Prophylaxis should be continuous on a year-round basis with no rest periods. (3) The rheumatic is at greatest risk when he is frequently exposed to children under 12, since streptococcus disease is most common in such individuals. (4) Prophylaxis should be continued for several years after the attack of rheumatic fever.

The exact definition of duration has been the point of disagreement. There is no reason, theoretically, for ever withdrawing prophylaxis. Since lifetime chemotherapy is difficult to accomplish, various limits have been set. Age 18 has been recommended by the American Heart Association (23). This is a reasonable compromise provided the individual is, at that time, no longer in close association with children. School teachers, parents of young children and workers in the various fields of medicine may remain at risk for much longer periods. Prophylaxis should not terminate at an arbitrary age but be tailored to the needs of specific patients.

The daily ration of sulfonamide has been standardized at 0.5 Gm for small children or 1 Gm for older children and adults. A sulfapyrimidine (sulfadiazine, sulfamerazine, sulfamethazine) should be employed.

The optimal dose of penicillin for oral prophylaxis has not been determined. Most authorities recommend 200,000 units

twice daily. The first dose should be taken before breakfast, the second at any time during the evening. Buffered tablets of penicillin G are least expensive and entirely satisfactory. It is hoped that this type of prophylaxis will receive further study because it is almost certain that a single morning dose of this size per day will prove to be adequate. A single monthly intramuscular injection of 1,200,000 units of repository benzathine penicillin is appropriate when it is to be used in parenteral prophylaxis.

TREATMENT.—Recent studies have demonstrated that adequate treatment of group A hemolytic streptococcus respiratory infection with penicillin will prevent the development of rheumatic fever both in healthy and in rheumatic subjects (24, 25). This important observation is of inestimable value when a streptococcus infection develops in a person who has had rheumatic fever. Management of such patients without continuous prophylaxis, using a regime based on the treatment of streptococcus infection as it occurs, is not recommended. Approximately 50% of such infections fully capable of inciting a rheumatic recrudescence are inapparent or so atypical as to defy detection without bacteriologic study of the respiratory flora.

When a streptococcus infection does supervene in an unprotected individual, penicillin should be administered in bactericidal amounts for seven to 10 days. This may be accomplished by giving 1,000,000 units of buffered penicillin by mouth, or 300,000 units of procaine penicillin by injection daily. A single injection of 1,200,000 units of benzathine penicillin will probably be proved to be satisfactory for this purpose; this therapeutic technique has not been fully evaluated.

Antibiotics of the tetracycline group should not be used in the treatment of streptococcus infection unless the patient has been sensitized to penicillin, because these drugs do not effectively prevent the development of rheumatic fever (26). Erythromycin may be valuable for this purpose, but recommendations must await further clinical trials.

TREATMENT OF CONGESTIVE HEART FAILURE

Dyspnea, rales in the chest, venous distention and tenderness in the right upper quadrant caused by hepatic engorgement are

the usual signs of congestive heart failure in rheumatic fever. Peripheral edema is much less common. Adequate treatment requires control of the myocarditis which is accomplished by rest and the administration of anti-inflammatory drugs. Often this is all that is required, although sodium intake should be restricted at the first sign of failure. It has not yet been determined whether adrenocortical hormones offer any advantages over salicylate therapy in the presence of severe myocarditis. In this situation corticotropin may well be administered in full dosage after sodium intake has been reduced to a low level if the physician is willing to accept the hazard of salt and water retention and the hypertension which may be associated with the use of this agent.

If these measures do not control the process and restore cardiac compensation, the patient should be digitalized. The effects of the cardiac glycosides in improving the efficiency of the myocardium damaged by rheumatic fever have been debated, but current opinion is that they are of considerable value. Earlier attempts to use these drugs may have failed because it was not appreciated that the effective dose for children is approximately 50% greater than for adults.

Mercurial diuretics are extremely useful in the management of congestive heart failure in the rheumatic patient who does not respond to the foregoing measures or whose edema increases under adrenocortical hormone therapy. They should be used freely when indicated in the usual doses for adults and in one-half amounts for children.

Pericarditis is a common condition in severe rheumatic fever but rarely results in the accumulation of sufficient fluid to embarrass the heart. Aspiration of pericardial fluid is almost never required.

Oxygen therapy may be of real benefit in the individual with rheumatic myocarditis who has marked pulmonary congestion, dyspnea and cyanosis. It probably has no effect on the course of the disease and it is to be avoided unless the indications for its use are clear, since it adds greatly to the cost and complexity of care and the emotional impact of the illness.

Rehabilitation

A recent study by the San Francisco Heart Association has revealed that patients with rheumatic heart disease have a shocking lack of information about their disease and the measures which they should take to preserve their health and to prolong their lives. Only a few had ever heard of the importance of streptococcus infection, its prophylaxis or the value of early penicillin treatment. Virtually none had had any sort of work-counseling service. This situation represents a failure of the medical profession.

The author believes that the rheumatic patient, like the syphilitic, should never be without the services of an informed personal physician who will assume responsibility for his guidance after he has recovered from the acute illness. Preferably, of course, the same physician should have been in charge from the onset of the disease, but this is often impossible if hospital or convalescent home care has been required.

The first phase of rehabilitation involves the period of gradual return to full activity, during which time the patient, particularly if an adult, must be urged to do more, and his anxiety must be allayed. In the case of children, parents must be interviewed and an appropriate emotional climate established in the home. The usual concern and overprotectiveness should be avoided.

During this period the chemoprophylactic regimen instituted earlier is made a regular part of the individual's daily life. When complete return to normal activity has been attained the cardiac status should be evaluated with special reference to the presence of valvular heart disease. No limitations of any kind need be imposed if valvular disease is minimal or not present. Patients with more advanced disease should receive work-counseling service in an attempt to fit their jobs to their hearts. Such individuals should forego hard physical work and intense competitive sports. Usually they are fully able to do light and sedentary work and to be gainfully employed, to go to school and to enjoy mild outdoor activities such as walking or golf.

For the first five years after an acute attack of rheumatic fever the patient should visit the physician frequently enough for the doctor to make certain that chemoprophylaxis is maintained.

Constant encouragement may be required, and a regime based on a monthly administration of benzathine penicillin may prove to be most satisfactory. Physical examination should be performed once or twice a year to evaluate the cardiac status. If prophylaxis is discontinued the patient must be educated to report every respiratory infection with any sore throat to the physician so that streptococcus infection can be recognized and treated with penicillin.

CONCLUSION

The diagnostic, therapeutic and prophylactic techniques that have been described have changed the outlook for the patient with rheumatic fever. No longer must the physician helplessly watch the inexorable progress of the disease in the face of uncontrolled acute illness or repeated recurrences. Future generations of children will be spared much of the disability accompanying the acute and chronic phases of rheumatic fever. In addition, there surely will be a further decline in its frequency and severity. Physicians can confidently look forward to the time when this disorder will no longer be a major medical and health problem.

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